RO 205-3859

NEORECORMON® (EPOETIN BETA)

BRIEFING PACKAGE FOR THE FDA ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

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1. EXECUTIVE SUMMARY

The purpose of this document is to provide information to the FDA and the Oncologic Drugs Advisory Committee concerning data from a recently published study, MF4449 - *A Multicenter, Randomized, Double-blind Clinical Trial to Investigate the Effect of a 7-9 Week Period of Treatment with NeoRecormon® (epoetin beta) Compared with Placebo on Locoregional Tumor Control Following Radiotherapy in Patients with Head and Neck Tumors* (Henke, et al - Lancet. 2003; 362:1255-60). In addition, the document provides a comprehensive analysis of data from other Roche oncology trials using epoetin beta.

Epoetin beta has a well-established favorable benefit-risk profile in the treatment of patients with cancer. Epoetin beta is approved in the European Union for the following indications: the treatment of renal anemia in patients on dialysis and patients not yet undergoing dialysis; the prevention of anemia of prematurity; the prevention and treatment of anemia in patients with solid tumors treated with high-dose platinum-based chemotherapy; increasing the yield of autologous blood from patients in a predonation program, and treatment of anemia in patients with multiple myeloma, low-grade non Hodgkin's lymphoma or chronic lymphocytic leukemia.

Data from study MF4449 showed decreased local progression free survival in head and neck cancer patients treated with radiation therapy and epoetin beta compared to patients receiving radiation therapy with placebo. These findings contrasted with previous clinical experience in cancer patients with anemia. To assess if the findings in this study indicated a change in the benefit-risk profile in cancer patients receiving epoetin beta, a comprehensive review of preclinical and clinical data was performed by Roche. The clinical review of Roche data with epoetin beta included:

- Analysis of study MF4449 to evaluate prognostic factors and their potential impact on the study outcome.
- Meta-analysis of the overall clinical data in controlled trials of epoetin beta in cancer patients conducted by Roche.
- Extended survival follow-up in study MF4467 which was a large randomized trial of epoetin beta in patients with hematologic malignancies.

This briefing document focuses on these three points. The key findings from these analyses are summarized below.

Analysis of MF4449

The primary analysis showed a statistically significant decreased local progression free survival for those patients randomized to epoetin beta compared to placebo for the intent-to-treat (ITT) population. However, imbalances in important baseline covariates may have confounded the study.

- Subgroup analyses showed a higher rate of death in patients with tumors in the hypopharyngeal location in the epoetin beta group compared to the placebo group. There was almost no effect on survival in the non-hypopharyngeal locations.

- Differences in prognostic factors were most pronounced in the subgroup of patients with hypopharyngeal cancer. Baseline imbalances, such as differences in smoking status and TNM status, in this subgroup resulted in more patients with a worse prognosis in the epoetin beta treatment group. In the patients with non-hypopharyngeal cancer, the same characteristics were balanced, and there were no differences in treatment effect.

- The negative effect was seen primarily in strata 2 (incompletely resected tumors) and 3 (radiation only) patients and not in stratum 1 (completely resected) patients. Also, the negative effect was seen in patients with baseline hemoglobin values above 11 g/dL whereas a benefit was seen in patients with baseline hemoglobin less than 11 g/dL.

Meta-analysis of epoetin beta controlled trials

A meta-analysis was performed on pooled results from nine controlled clinical trials including 1409 patients with solid organ or hematological tumors to assess survival and tumor progression. Overall, there was no evidence of an untoward effect on either survival or progression for cancer patients treated with epoetin beta.

- There was no difference between the patients treated with epoetin beta and control for overall survival (HR=0.97).

- The hazard ratio for progression of cancer with epoetin beta was 0.79 compared to control in a meta-analysis of the available clinical data.

- There was a small increase in the incidence of thromboembolic events in cancer patients receiving epoetin (6% on epoetin beta versus 4% on placebo) which is addressed in the product label. The higher crude rate for epoetin beta compared to control disappears when normalized for patient years of observation.

Survival update of MF4467

In order to obtain longer term follow-up on survival than available in the meta-analysis, a survival update was conducted for study MF4467 - *A Double-blind, Placebo-controlled Study of NeoRecormon® (epoetin beta) in the Treatment of Anemia in Patients with Lymphoid Malignancies*. There was no difference in survival between patients treated with epoetin beta and placebo. These data provide additional evidence that treatment with epoetin beta does not have an untoward effect which manifests late in the treatment of cancer patients.

- There were 170 patients in the epoetin beta treatment group and 173 patients in the placebo group included in this analysis.

- The Kaplan-Meier curves for overall survival were similar in both treatment groups. The logrank test did not indicate differences in survival between the groups (p=0.76).

- Median survival was 17.4 months in the epoetin beta and 18.3 months in the placebo group.

2. SUMMARY OF STUDY MF4449

2.1 Methods

The objective of study MF4449 was to investigate whether the efficacy of radiotherapy in patients with head and neck tumors can be improved by correction or partial correction of anemia with epoetin beta compared with a placebo treatment. This study was conducted in Europe. Patients were required to have advanced stage (III/IV) squamous cell carcinoma of the head and neck. The patients were to either receive postoperative radiation therapy (RT) or scheduled to undergo definitive radiotherapy alone. Patients were required to have a baseline hemoglobin below 12 g/dL for women or below 13 g/dL for men. Patients were required to have a performance status of 60 or more (Karnofsky). Exclusion criteria were refractory hypertension, thrombocytosis, epilepsy, other concomitant malignant disease, pregnancy or inadequate contraception, participation in another protocol within 6 weeks, or treatment with any cytostatic drug within 3 months.

Patients were randomized to either epoetin beta or placebo. Randomization was stratified according to three strata based on postoperative margins. Stratum 1 was patients with completely resected tumors, stratum 2 was patients with incompletely resected tumors, and stratum 3 was patients with radiotherapy only. Patients received either placebo or epoetin beta 300 IU/kg subcutaneously three times per week, starting two weeks before the planned radiotherapy, if possible. Treatment was continued until hemoglobin levels exceeded 14 g/dL for women or 15 g/dL for men, or if hemoglobin increased by more than 2 g/dL in one week. Treatment was resumed when hemoglobin fell below target levels. Patients were treated with the study medication until the end of radiotherapy (i.e. generally 7-9 weeks). Oral iron therapy was started 10-14 days before treatment or iron therapy was administered intravenously if the patients' serum transferrin fell below 25%. At the end of the treatment phase and when radiotherapy finished, a follow-up phase started.

Standard or three-dimensional planning techniques for radiotherapy were allowed as long as the same approach was used for all patients at the site. The tumor volume plus a 2-3 cm margin and nodes were included in the treatment field using standard dose and fractionation techniques. A total of 60 Gy was prescribed for resected tumors and 70 Gy for macroscopically incompletely resected tumors or primary definitive therapy.

The primary endpoint was locoregional progression-free survival (LPFS). Secondary endpoints included survival rate, time to onset of local tumor progression or death, and increases in hematologic values which included: hemoglobin, hematocrit, red blood cell count, reticulocyte count, and selected parameters of iron sufficiency.

2.2 Results

2.2.1 Patient Population Characteristics

A total of 351 patients were randomized and enrolled between March, 1997 and April, 2001. This study was started in 1997 and the follow-up period ended in 2002. Data

analyses were completed in April, 2003. An overview of the baseline patient demographics is shown in Table 1 below.

Table 1 Demographic Data

	PLACEBO N = 171	EPOETIN BETA N = 180
Sex		
MALE	145 (85%)	158 (88%)
FEMALE	26 (15%)	22 (12%)
n	171	180
Age in years		
Mean	56.9	58.0
SD	9.63	8.97
SEM	0.74	0.67
Median	57.0	58.0
Min-Max	36 - 87	35 - 81
n	171	180
Weight in kg		
Mean	67.64	67.19
SD	14.266	13.245
SEM	1.091	0.987
Median	65.50	67.00
Min-Max	40.0 - 113.0	42.0 - 115.0
n	171	180
Height in cm		
Mean	172.0	172.2
SD	7.76	7.45
SEM	0.60	0.56
Median	172.0	172.0
Min-Max	150 - 194	155 - 198
n	168	179
Does Subject Consume Tobacco?		
NO	79 (46%)	62 (34%)
NOT KNOWN	1 (<1%)	-
YES	91 (53%)	118 (66%)
n	171	180
SBP at Baseline (mmHg)		
Mean	127.5	128.2
SD	16.87	19.64
SEM	1.33	1.53
Median	126.0	125.0
Min-Max	80 - 180	65 - 182
n	161	164
DBP at Baseline (mmHg)		
Mean	77.4	77.5
SD	9.33	10.25
SEM	0.73	0.80
Median	80.0	80.0
Min-Max	50 - 100	50 - 100
n	161	164

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

The only imbalance in baseline characteristics was smoking status which will be discussed further in Section 2.2.5. Information on baseline hematology values is provided below.

Table 2 Baseline Hemoglobin

Parameter	STATISTIC	PLACEBO	EPOETIN BETA
Hemoglobin [g/dL]	N	170	180
	MEAN	11.7	11.6
	SD	1.2	1.1
	MIN	6.9	8.5
	Q1	11.0	10.9
	MEDIAN	11.8	11.7
	Q3	12.6	12.5
	MAX	14.6	14.4
Hematocrit [%]	N	170	180
	MEAN	35.6	35.4
	SD	3.6	3.6
	MIN	23.7	26.0
	Q1	33.4	33.1
	MEDIAN	35.7	35.7
	Q3	38.1	37.9
	MAX	43.1	44.6
Erythrocytes [10**12/L]	N	169	180
	MEAN	3.9	3.8
	SD	0.4	0.4
	MIN	2.5	2.7
	Q1	3.6	3.6
	MEDIAN	3.9	3.8
	Q3	4.2	4.1
	MAX	5.5	5.2
Reticulocytes [x10E3/uL]	N	150	155
	MEAN	62.8	63.3
	SD	41.5	50.0
	MIN	4.2	4.0
	Q1	35.6	38.3
	MEDIAN	54.6	54.1
	Q3	76.2	76.3
	MAX	221.0	506.8
Serum EPO Level [U/L]	N	122	135
	MEAN	17.6	17.8
	SD	22.4	39.9
	MIN	3.3	11.0
	Q1	11.0	11.0
	MEDIAN	11.0	11.0
	Q3	11.6	11.0
	MAX	168.1	446.2
O/P Ratio	N	121	135
	MEAN	0.8	0.8
	SD	0.2	0.2
	MIN	0.3	0.4
	Q1	0.7	0.6
	MEDIAN	0.8	0.7
	Q3	0.9	0.9
	MAX	1.6	1.7

2.2.2 Local Progression-free Survival

The primary endpoint, local progression-free survival (LPFS), was significantly shorter in the epoetin beta treatment group compared to the placebo group for the intent-to-treat (ITT) population. The number of events (death and local progression) in the epoetin beta group was higher than in the placebo group (Table 3). The risk of local progression or death was higher in the epoetin beta group than in the placebo group for the ITT population (adjusted hazard ratio (HR)=1.62; Wald χ^2 test p=0.0008).

Table 3 Overview of Local Progression-free Survival Results

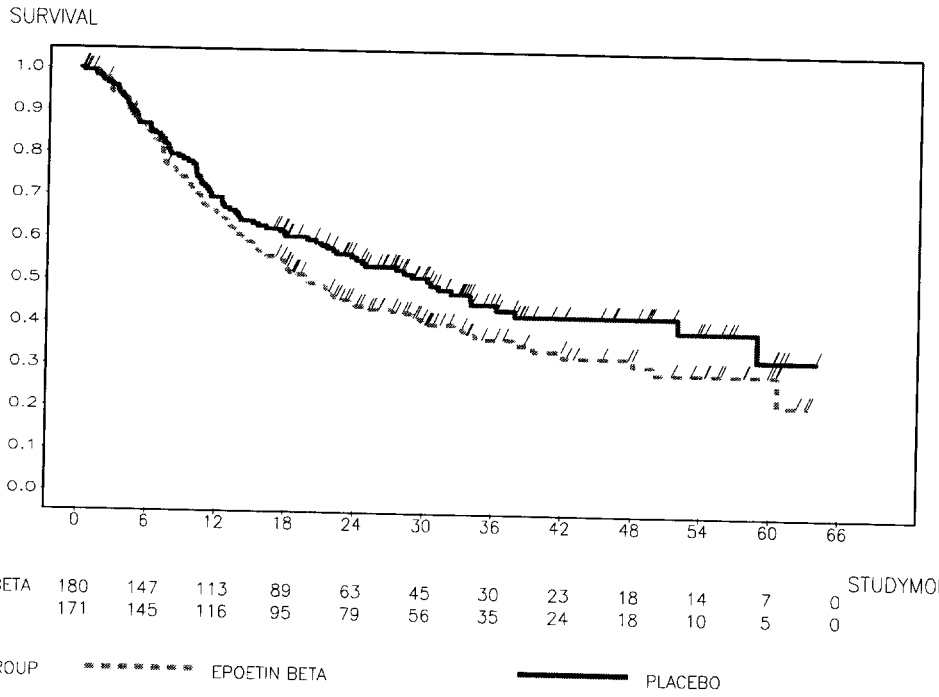
	EPOETIN BETA		PLACEBO
Total Number of Patients	180		171
Number of Events	116		92
Number of Censored Cases	64		79
Percentage of Censored Cases [%]	35.56		46.20
Q1 (Observation Time) [days]	190		214
Median Observation Time [days]	406		745
Q3 (Observation Time) [days]	1793		.
Treatment effect			
Adjusted Cox analysis Epoetin Beta vs. Placebo	1.616	[1.22;2.14]	0.0008
p-Value (Log Rank test)			0.0415

2.2.3 Survival

The Kaplan-Meier plot for the survival time for the ITT population is shown in Figure 1. The curves between the placebo and the epoetin beta treatment groups appear to diverge 6 months after the start of the treatment.

Figure 1 Survival Time - ITT Population

edd21_2001 – Survival Time by Trial Treatment
Protocol: MF4449
Analysis: INTENT-TO-TREAT POPULATION
Filter applied: WHERE ECTYPEN LE 2



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Overall there were more deaths in the epoetin beta treatment group (61%) than in the placebo group (52%). An overview of the deaths are presented in tables 4 and 5. An equal percentage of patients (34%) died in the placebo and epoetin beta treatment groups due to benign and malignant neoplasms. More patients died in the epoetin beta treatment group

due to cardiac disorders (10 cases vs. 5 cases in the placebo group) and general disorders (9 vs. 1 in the placebo group).

Table 4 Summary of Deaths

Cause of Death	PLACEBO N = 171 No. (%)	EPOETIN BETA N = 180 No. (%)
Total No. of Deaths	89 (52)	109 (61)
BENIGN & MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)	58 (34)	61 (34)
VASCULAR DISORDERS	10 (6)	7 (4)
CARDIAC DISORDERS	5 (3)	10 (6)
GENERAL DISORDERS	1 (<1)	9 (5)
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS	6 (4)	4 (2)
INFECTIONS & INFESTATIONS	3 (2)	5 (3)
GASTROINTESTINAL DISORDERS	2 (1)	5 (3)
DISORDERS OF METABOLISM & NUTRITION	1 (<1)	3 (2)
HEPATO-BILIARY DISORDERS	1 (<1)	2 (1)
NEUROLOGICAL DISORDERS	1 (<1)	1 (<1)
PSYCHIATRIC DISORDERS	1 (<1)	1 (<1)

Percentages are based on N. Percentages not calculated if N < 10.

Table 5 Summary of Time to Event Analysis (Death) - ITT Population

	PLACEBO	EPOETIN BETA
Total Number of Patients	171	180
Number of Events	89	109
Number of Censored Cases	82	71
Percentage of Censored Cases [%]	47.95	39.44
Q1 (Observation Time) [days]	308	260
Median Observation Time [days]	928	605
Q3 (Observation Time) [days]	.	1843
p-Value (Log Rank test)		0.0901

A multivariate analysis was performed in order adjust for stratification factors. The risk of death in the adjusted analysis was higher in the epoetin beta group than in the placebo group (adjusted HR=1.39; Wald χ^2-test p=0.0231; Table 6).

Table 6 Summary of Cox Regression Analysis of Survival Time - ITT Population

Factor	For	Relative Risk	95 % Confidence Interval	p-Value
Treatment Effect	Epoetin Beta vs. Placebo	1.387011	[1.05;1.84]	0.0231
Stratum	2,3 vs. 1	1.563411	[1.08;2.26]	0.0175
Stratum	3 vs. 1,2	2.929563	[1.99;4.31]	<.0001
TNM-Staging	IV vs. I,II,III	1.415019	[1.00;2.00]	0.0497

There is a relevant difference between the logrank test and the result of the adjusted Cox regression model in terms of testing the overall treatment effect (logrank test, p=0.09, adjusted Cox model, p=0.023). The primary analysis was defined as adjusted by stratum (i.e. resection status defined as 1: complete surgery, 2: incomplete surgery and 3: no surgery) and TNM staging. The difference between the unadjusted logrank test in table 5 and the adjusted Cox regression analysis in table 6 is explained by the heterogeneity of study outcome across the different strata, especially with respect to the 25% of patients in stratum 2, in which the most prominent treatment difference was observed in contrast to the 50% of patients in stratum 1, in which no treatment difference was noted. In an adjusted analysis the weighting for stratum 2 patients is increased compared to an unadjusted analysis, leading ultimately to the different p-values.

2.2.4 Hematologic parameters

There was an increase in the mean hemoglobin concentration from baseline up to week 6 of epoetin beta treatment, after which hemoglobin concentration remained unchanged up to week 9. Hemoglobin response to treatment is summarized in the table below.

Table 7 Summary of hemoglobin over time

Treatment Group	STATISTIC	Base-line	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Last value
PLACEBO	N	170	162	157	161	155	158	158	155	140	94	168
	MEAN	11.7	0.2	0.4	0.4	0.7	0.9	0.9	0.9	0.9	0.9	0.9
	SD	1.2	0.8	0.9	1.1	1.3	1.3	1.3	1.5	1.6	1.9	1.7
	MEDIAN	11.8	0.2	0.4	0.4	0.6	0.9	0.9	0.8	0.8	1.0	1.0
	MIN	6.9	-3.0	-3.8	-4.4	-2.7	-2.6	-3.2	-3.6	-4.1	-4.8	-3.6
	MAX	14.6	2.5	3.0	3.3	4.9	4.9	5.2	6.8	6.2	6.3	6.3
EPOETIN BETA	N	180	169	167	165	165	166	169	160	140	101	178
	MEAN	11.6	0.9	1.9	2.5	2.9	3.3	3.3	3.4	3.4	3.6	3.4
	SD	1.1	0.8	1.1	1.3	1.5	1.5	1.6	1.6	1.6	1.7	1.7
	MEDIAN	11.7	0.9	2.0	2.5	3.0	3.5	3.4	3.4	3.4	3.8	3.5
	MIN	8.5	-2.1	-2.9	-2.1	-1.9	-2.1	-1.7	-1.6	-2.4	-1.5	-2.4
	MAX	14.4	2.9	4.5	5.1	6.1	6.1	7.3	7.3	6.8	7.6	7.8

2.2.5 Prognostic Factors Contributing to Outcome

Smoking Status

Overall, the study was well balanced across the major prognostic factors with the exception of smoking status. In the epoetin beta group, 66% of the patients were smokers while 53% of patients in the placebo group were smokers. This 13% difference in smoking status confounded the results, and could explain in a multivariate analysis roughly 30% of the difference in favor of the placebo group.

Contribution of Tumor Location

Subgroup analysis showed a higher rate of death in patients with tumors in the hypopharyngeal location in the epoetin beta group compared to the placebo group

(Figure 2 and Figure 3). The high rate of death in patients with hypopharyngeal cancer had a major impact on the overall outcome of the study.

Figure 2 Survival in Patients with Non-hypopharyngeal Cancer

edd21_2013 - Survival Time by Trial Treatment
Protocol: MF4449
Analysis: INTENT-TO-TREAT POPULATION - OTHER LOCATION THAN HYPOPHARYNX
"Filter applied: WHERE ECTYPEN LE 2 AND HYPOPHAR = "NO"

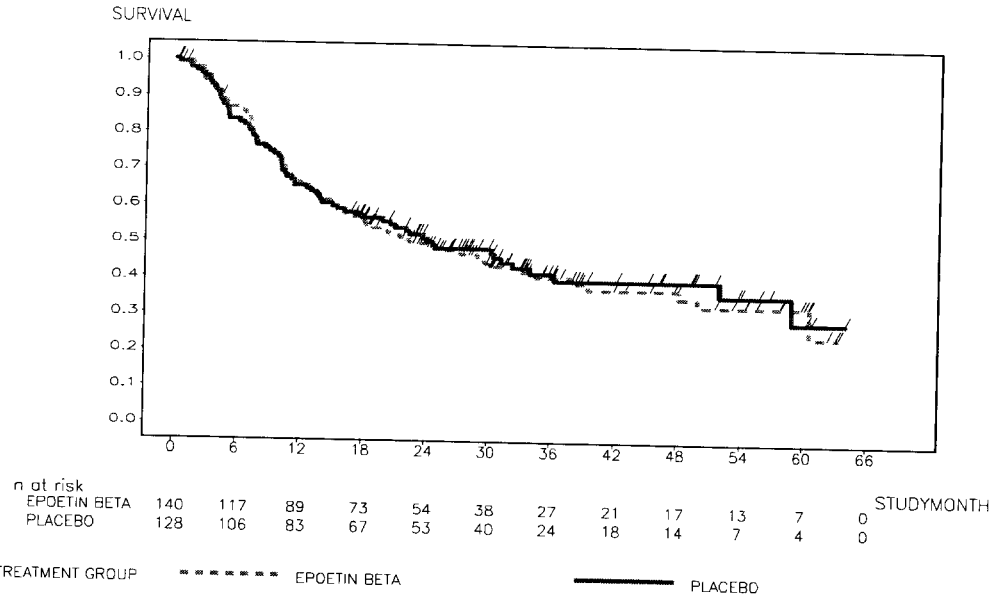

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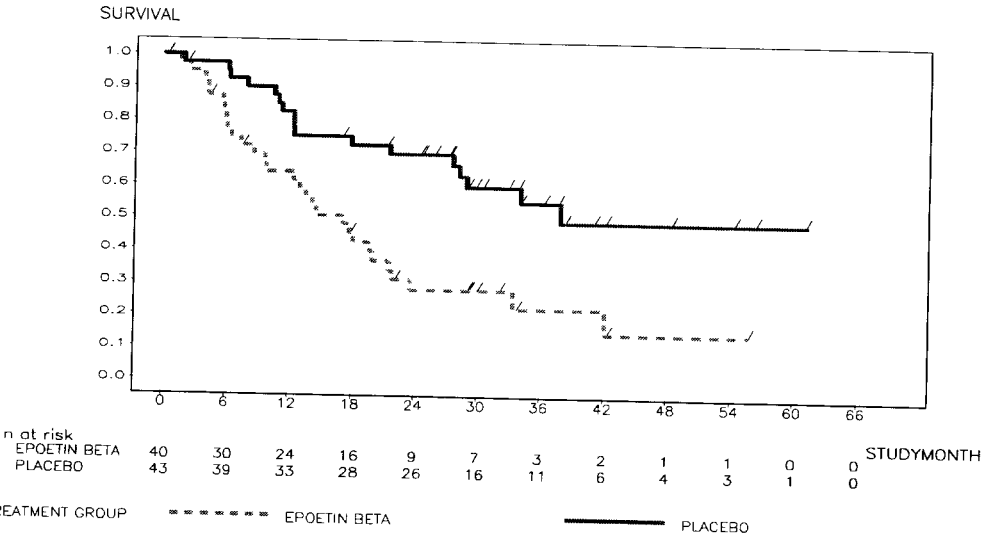
Figure 3 Survival in Patients with Hypopharyngeal Cancer

edd21_2011 - Survival Time by Trial Treatment
Protocol: MF4449
Analysis: INTENT-TO-TREAT POPULATION - HYPOPHARYNX
Filter applied: WHERE ECTYPEN LE 2 AND HYPOPHAR = YES'



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In Figure 2, the lack of difference in survival in patients with non-hypopharyngeal cancer is apparent. To further evaluate the potential effect in the subset of patients with hypopharyngeal cancer, prognostic factors at baseline were checked for clinically relevant imbalances in the study, and also in this subset.

Tumor Grade

The number of patients with stage IV disease was balanced for the overall study (75% on epoetin beta versus 72% on placebo). However, in the subgroup of patients with hypopharyngeal cancer, 85% of patients on epoetin beta were stage IV compared to 70% on placebo. In addition to baseline stage, there was a difference in the percentage of patients receiving definitive radiotherapy only in the hypopharyngeal subgroup. The data for treatment stratum in the hypopharyngeal subgroup are shown below in table 8.

Table 8 Treatment Stratum and Resection Margin Status of Hypopharynx Subgroup

	PLACEBO N = 43	EPOETIN BETA N = 40
Treatment Stratum		
STRATUM 1 (R0)	21 (49%)	18 (45%)
STRATUM 2 (R1 + R2)	9 (21%)	4 (10%)
STRATUM 3 (Rx only)	13 (30%)	18 (45%)
n	43	40
Resection Margin Status		
R0	21 (70%)	18 (82%)
R1	8 (27%)	3 (14%)
R2	1 (3%)	1 (5%)
n	30	22

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

Of note, in the subgroup of patients with hypopharyngeal cancer, 45% of patients were from stratum 3, defintive radiotherapy only compared to 30% in this stratum for placebo. This imbalance favors the placebo treatment group as the radiation therapy only group clearly has the worst prognosis.

Baseline Hemoglobin

The overall negative effect on local progression free survival was primarily seen in patients with baseline hemoglobin values above 11 g/dL. A benefit was seen in patients with baseline hemoglobin less than 11 g/dL.

Treatment of the Tumor

Another possible explanation for the finding is that there were differences in the treatment administered to the two groups with regards to radiotherapy. Overall, no apparent differences in radiotherapy treatment were seen between the two treatment groups. An assessment of outcome in the radiotherapy correct population was performed. Outcome differences were of much lower magnitude in the radiotherapy correct population (RCP) than in the ITT population. This, together with the large proportion of patients with incorrect radiotherapy by protocol, lead to the initial hypothesis that the treatment differences seen in the ITT population could be the result of protocol violations

related to incorrectly administered RT doses. Blinded review by an independent expert suggested that the incorrect radiotherapy was unlikely to account for the difference in local progression free survival between the two treatment groups.

2.3 Safety

This section includes a summary of the adverse events that were reported with a specific focus on thromboembolic events. An overview of the adverse events is provided in table 9 below.

Table 9 Overview of safety

	PLACEBO (N = 171)	EPOETIN BETA (N = 180)
Any Non-Cancer related AE	111 (64.9%)	123 (68.3%)
Any Cancer Related AE	78 (45.6%)	92 (51.1%)
Serious AE	39 (22.8%)	47 (26.1%)
Related AE	10 (5.8%)	15 (8.3%)
Serious Related AE	0 (0.0%)	3 (1.7%)
AE due to Radiotherapy	66 (38.6%)	84 (46.7%)
AE leading to Withdrawal (excl deaths due to AE)	8 (4.7%)	8 (4.4%)
Death	89 (52.0%)	108 (60.0%)

The occurrence of adverse events and serious adverse events was generally balanced between the two treatment groups. There was no difference in the adverse events leading to treatment withdrawal. The frequency of adverse events due to radiotherapy was higher on the epoetin beta arm.

2.3.1 Adverse events

Table 10 summarizes the non-cancer related adverse events. The most common adverse events were general disorders (mucosal inflammation due to radiotherapy treatment) followed by skin and subcutaneous tissue disorders (mainly skin reactions also due to radiotherapy treatment) occurring with a slightly higher incidence in the epoetin beta treatment group, gastrointestinal disorders occurring with an equal incidence in both groups, and infections and infestations occurring with a slightly higher incidence in the placebo group compared to the epoetin beta treatment group. The percentages of patients with adverse events relating to disorders of blood and the lymphatic systems, and vascular disorders (e.g hypertension, thromboembolic events) were higher in the epoetin beta treatment group compared to the placebo group. Adverse events relating to respiratory, thoracic and mediastinal disorders were higher in the placebo group compared to the epoetin beta group. All other adverse events occurred with almost equal and low incidence in both groups.

Table 10 Summary of Non-cancer Related Adverse Events

Body System/ Adverse Event	PLACEBO N = 171 No. (%)	EPOETIN BETA N = 180 No. (%)
ALL BODY SYSTEMS	111 (65)	123 (68)
GENERAL DISORDERS	43 (25)	54 (30)
SKIN & SUBCUTANEOUS TISSUE DISORDERS	37 (22)	43 (24)
GASTROINTESTINAL DISORDERS	34 (20)	37 (21)
INFECTIONS & INFESTATIONS	36 (21)	30 (17)
DISORDERS OF BLOOD & THE LYMPHATIC SYSTEM	13 (8)	23 (13)
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS	19 (11)	11 (6)
VASCULAR DISORDERS	9 (5)	19 (11)
INJURY & POISONING	6 (4)	7 (4)
NEUROLOGICAL DISORDERS	4 (2)	8 (4)
PSYCHIATRIC DISORDERS	7 (4)	5 (3)
HEPATO-BILIARY DISORDERS	6 (4)	4 (2)
MUSCULOSKELETAL, CONNECTIVE TISSUE & BONE DISORDERS	5 (3)	5 (3)
DISORDERS OF THE IMMUNE SYSTEM	3 (2)	7 (4)
DISORDERS OF METABOLISM & NUTRITION	3 (2)	6 (3)
CARDIAC DISORDERS	4 (2)	5 (3)
INVESTIGATIONS	4 (2)	3 (2)
DISORDERS OF THE EAR & LABYRINTH	5 (3)	2 (1)
DISORDERS OF THE EYE	4 (2)	3 (2)
SURGICAL & MEDICAL PROCEDURES	2 (1)	4 (2)
RENAL & URINARY DISORDERS	1 (<1)	3 (2)
ENDOCRINE DISORDERS	1 (<1)	1 (<1)

Percentages are based on N. Percentages not calculated if N < 10.
Multiple occurrences of the same adverse event in one individual counted only once.

2.3.2 Thromboembolic events

The proportion of patients reporting at least one thromboembolic event was 6% (10/180) in the epoetin beta treated population compared with 4% (6/171) in the placebo treated population. Events reported included intestinal ischemia (1 in the placebo group), pulmonary embolism (1 in the placebo group and 2 in the epoetin beta group) venous phlebitis (2 in the epoetin beta group), venous thrombosis (2 in the epoetin beta group), brain stem infarction (1 in the epoetin beta group), cerebrovascular accident (CVA, 1 in each group), angina (1 in each treatment group) and necrosis (2 in the placebo and 1 in the epoetin beta group). The main difference between the groups lies in the incidence of minor thromboses including venous phlebitis and thrombosis. The reported incidence of more serious thromboembolic events was extremely low. One subject with a confirmed brain stem infarction had developed a marked thrombocytosis following epoetin treatment shortly before the event. Two subjects died as a result of a CVA; one in each group. There were no deaths attributed to thromboembolic processes other than these.

2.4 Discussion

Multiple factors could account for the adverse outcome with regards to survival found in the trial. The most striking finding is that the higher rate of death in the epoetin beta treatment group is limited to patients with hypopharyngeal cancer. The differences in outcome are largely limited to patients with hypopharyngeal tumors where differences in baseline prognostic factors favored the placebo group. In contrast, outcomes among patients with non-hypopharyngeal cancer, in whom prognostic factors were more evenly

distributed at baseline, show no detrimental effects. The imbalances for prognostic factors identified in the hypopharyngeal subgroup may have confounded the trial.

3. POOLED ANALYSIS OF CANCER PATIENTS TREATED WITH EPOETIN BETA

A meta-analysis was done on pooled results from nine controlled clinical trials with epoetin beta including 1409 patients with solid organ or hematological tumors to assess survival and tumor progression. Study MF4449 was specifically designed to assess epoetin beta in the treatment of patients receiving radiotherapy, therefore the results from this study were not included in the meta-analysis.

3.1 Methods

The pooled analysis included nine controlled clinical studies performed by Hoffmann-La Roche or Boehringer Mannheim. The studies are summarized in Table 11.

Table 11 Overview of Studies Included in the Pooled Analysis

Study Number	Study Design	Diagnosis	No. of patients included in analysis (epoetin beta/control	Total patient year in study (epoetin beta / control)
MF4249	R O PG 3-arm	Ovarian cancer Anemia (Hb < 13 g/dL)	83 / 33	41.0 / 16.5
MF4250	R O PG 3-arm	MM or NHL (incl. CLL) Anemia (Hb < 10 g/dL) Transfusion dependent	95 / 49	40.0 / 20.4
MF4252	R PG	Rectal cancer	28 / 26	2.9 / 2.8
MF4253	R PC DB	Hemicolectomy due to carcinoma Anemia (Hb 8.5 – 13.5 g/dL)	52 / 57	5.3 / 6.0
MF4266	R O PG	AML	10 / 10	3.4 / 5.2
MF4313	R O PG dose finding	MM, NHL or CLL Anemia (Hb ≤ 11 g/dL) Transfusion independent	117 / 29	26.5 / 6.6
MF4321	R PG	Solid organ tumors Anemia (Hb < 11 g/dL)	114 / 104	41.7 / 27.1
MF4421	R O PG	Malignant disease Anemia (Hb < 11 g/dL)	131 / 128	36.3 / 37.5
MF4467	R PC DB PG	MM, NHL or CLL Anemia (Hb < 10 g/dL) Transfusion dependent Erythropoietin deficiency	170 / 173	58.1 / 59.4

R = randomized, C = controlled, PC = placebo controlled, DB = double-blind, PG = parallel-group, O = open label
Hb = hemoglobin

The studies were not designed to assess duration of survival, therefore, no follow-up for survival was done beyond study treatment plus a 28 day follow-up period in all but one study. During the 28 day follow-up period serious adverse events including deaths were recorded. Deaths reported later were not included in this analysis, as follow-up data were not consistently collected after the standard 28 day period. Censoring for survival for patients without events was defined as the last entry in the drug-log plus 28 days. In one study, (MF4321) 29 patients received placebo in the first treatment phase and epoetin beta in the second phase. These patients were censored at the time of initiation of epoetin beta treatment (Day 84).

Assessment of tumor status was not part of the protocol in any of the nine studies, but reports of malignancy progression were part of the Adverse Event recording. In order to retrospectively assess time to malignancy progression, all adverse events were carefully reviewed for malignancy progression. Reviewers were blinded to treatment assignment. Reports of symptoms that could be linked to malignancy progression by a clear remark in the text written by the investigator, or in additional comments, were flagged as malignancy progressions on the database. The onset date of the earliest of these events was used as the time of the first notice of tumor progression. Events were included in the analysis if observed during study treatment or during the standard 28 day follow up period. Patients without events were censored as for survival at the time of last entry into the drug log plus 28 days.

3.2 Results

3.2.1 Patient Population Characteristics

3.2.1.1 Demographic Characteristics

In the pooled population, the two treatment groups are well balanced with regard to demographic characteristics (see table 12).

Table 12 Demographic Information in the Pooled Population

	CONTROL N = 609	EPOETIN BETA N = 800
Sex		
MALE	247 (41%)	320 (40%)
FEMALE	362 (59%)	480 (60%)
n	609	800
Race		
CAUCASIAN	465 (97%)	612 (98%)
BLACK	-	-
ORIENTAL	-	-
OTHER	12 (3%)	13 (2%)
n	477	625
Age in years		
Mean	60.8	61.1
SD	11.83	12.39
SEM	0.48	0.44
Median	62.0	63.0
Min-Max	19 - 91	20 - 87
n	609	800
Weight in kg		
Mean	67.32	66.79
SD	12.619	12.515
SEM	0.577	0.486
Median	66.40	66.00
Min-Max	40.0 - 112.0	35.0 - 118.0
n	478	663
Height in cm		
Mean	165.7	165.4
SD	9.14	8.86
SEM	0.37	0.31
Median	165.0	165.0
Min-Max	140 - 198	126 - 190
n	599	800

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

The duration of follow-up was a maximum of 6 months for almost all patients. The limited follow-up could result in missing an effect on progression at a later point, therefore, longer follow-up was obtained in one large study, MF4467 as described in section 4.

3.2.2 Malignant Disease

In the overall population, 56% of the patients had hematological malignancies and the remaining 44% were diagnosed with solid organ tumors. The five patients classified as "other" were diagnosed with Hodgkin's lymphoma. Tumor stage was not consistently collected in the various studies, since tumor treatment was not the outcome of any of these studies. Information on tumor stage (FIGO or TNM) was available in about three quarters of the patients with solid organ tumors. Although there are no obvious differences in tumor staging between the treatment groups, the data is difficult to interpret.

3.2.3 Hemoglobin at Baseline and During Treatment

Baseline hemoglobin levels were similar in the two groups in the pooled population with a mean hemoglobin level of 9.86 g/dL in the epoetin beta treatment group and 9.93 g/dL in the control group. Hemoglobin responses during treatment are summarized in Table 13. The mean baseline adjusted hemoglobin AUC was 1.01 g/dL in the epoetin

beta treatment group compared with 0.16 g/dL in the control group, indicating a difference in hemoglobin of about 1 g/dL during the study.

Table 13 Summary of Hemoglobin during Treatment by Trial Treatment

	CONTROL N = 609	EPOETIN BETA N = 800
Maximum of Hemoglobin During Study [g/dL]		
Mean	11.55	12.57
SD	1.743	2.275
SEM	0.071	0.081
Median	11.30	12.70
Min-Max	5.9 - 21.7	5.9 - 22.4
n	608	793
HGB AUC Baseline Adjusted [g/dL]		
Mean	0.16	1.01
SD	1.250	1.498
SEM	0.051	0.054
Median	0.10	1.00
Min-Max	-4.4 - 5.3	-4.3 - 6.2
n	594	783

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.

Information on concomitant cancer therapy and its start and outcome as well as previous cancer therapy were not generally recorded in any studies.

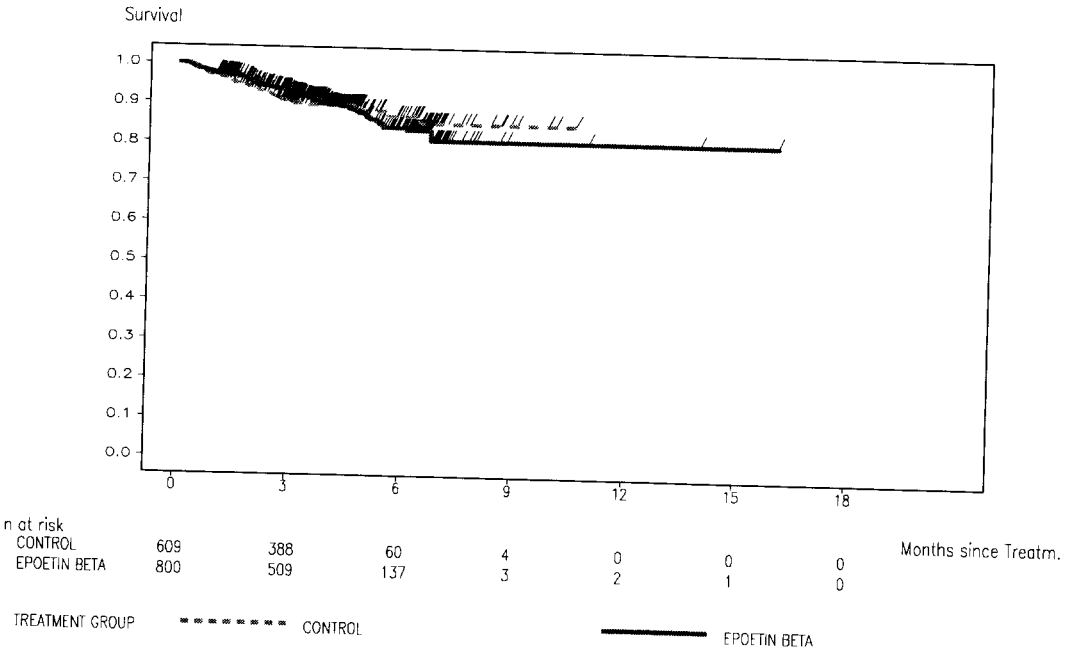
3.2.4 Survival

There were no differences in the number of deaths per patient year in the pooled population. The rate of death per patient year was slightly lower in the epoetin beta arm (3.13) compared with the control arm (3.36) in the pooled population. The average follow-up time per patients was 0.30 years in the control group and 0.32 years in the epoetin beta group. In the subgroup of patients with solid organ tumors, the number of deaths per patient year was slightly lower in the epoetin beta arm (3.16) compared with the control arm (3.98), while in the subgroup of patients with hematological tumors, the number of deaths per patient year was slightly higher in the epoetin beta arm (3.11) compared with the control arm (2.96).

The similar rate of survival in the two treatment groups was confirmed in a Kaplan-Meier analysis. The curves from the epoetin beta and control arms are broadly overlapping for the pooled population, as shown in Figure 4. The curves include all deaths occurring within 28 days after last dosing in order to ensure equal and consistent follow-up in both treatment arms.

Figure 4 Duration of Survival, Including All Deaths until Day 28 after End of Treatment

ekm21dd28_3030 – Duration of Survival – All Deaths within 28 Days after Treatment End
Protocol: CDP10130
Analysis: SAFETY POPULATION – CONTROLLED STUDIES
Filter applied: WHERE SAFCOD EQ 1 AND PROTO IN (MF4249 MF4250 MF4252 MF4253 MF4266 MF4313 MF4321 MF4421 MF4467)



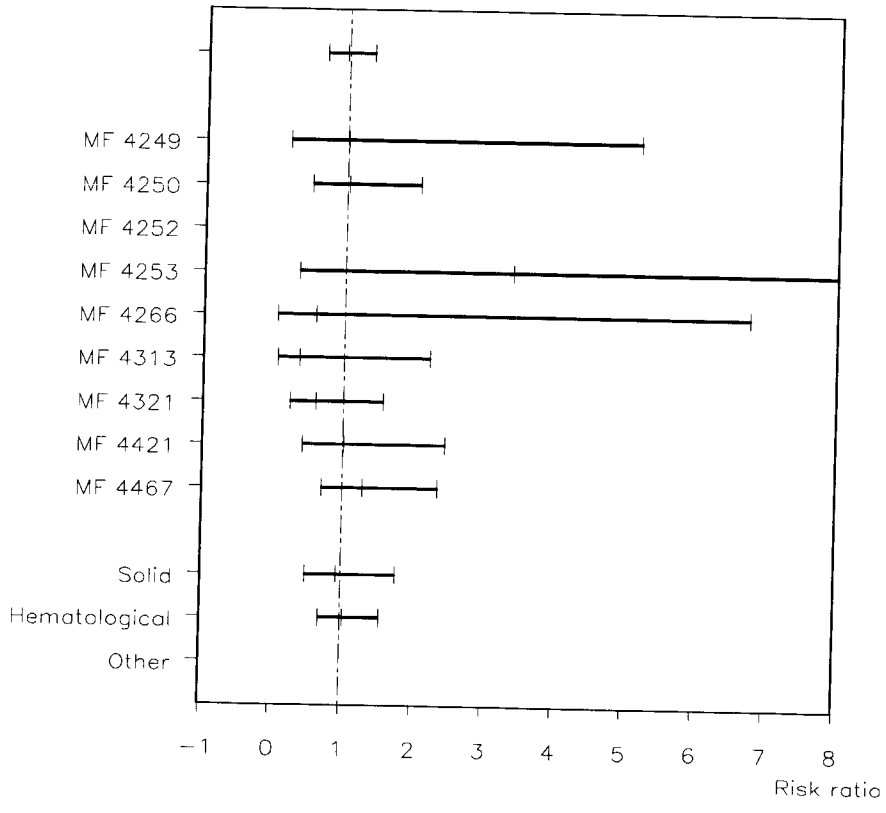
km21dd28: Produced by nendelv on 17MAR04

A summary of the underlying risks measured by the hazard ratio (relative risk) in all individual studies is provided in figure 6. There was no sign of increased risk of death after epoetin beta treatment in the pooled analysis, and there was also no signal in any of the individual studies. The hazard estimate appears high in study MF4253, but there were only 4 events in this study and the 95% confidence intervals are very broad, which does not indicate any trend. In study MF4252, there were not enough events to estimate a hazard rate. In three of the remaining eight studies the hazard ratio was about one, in three studies it was below one, and in two studies it was above one. The results in the subgroups of patients with solid organ tumors and hematological tumors were consistent with the overall results.

Figure 5 Summary of Hazard Rate (Kaplan-Meier Estimates and Cox Regression) Including all Deaths until Day 28 after end of Treatment

esurv21dd28_3030 Hazard Ratio and 95% Confidence Intervals for Overall Survival by Subgroup - Deaths until day 28

Protocol(s): CDP10130
Analysis: SAFETY POPULATION - CONTROLLED STUDIES
Filter applied: WHERE SAFCOD EQ 1 AND PROTO IN ('MF4249' 'MF4250' 'MF4252' 'MF4253' 'MF4266' 'MF4313' 'MF4321' 'MF4421' 'MF4467')



	N	Lower confidence limit	Estimate	Upper confidence limit
Total	1409	0.69	0.97	1.36
Study				
MF 4249	116	0.19	1.01	5.18
MF 4250	144	0.51	1.02	2.05
MF 4252	54	.	.	.
MF 4253	109	0.35	3.39	32.57
MF 4266	20	0.05	0.59	6.76
MF 4313	146	0.06	0.37	2.21
MF 4321	218	0.24	0.61	1.56
MF 4421	259	0.42	1.02	2.45
MF 4467	343	0.71	1.29	2.35
Tumor Class				
Solid	613	0.49	0.93	1.77
Hematological	791	0.69	1.04	1.55
Other	5	.	.	.

surv21dd28: Produced by nendelv on 17MAR04

3.3 Time to Malignancy Progression

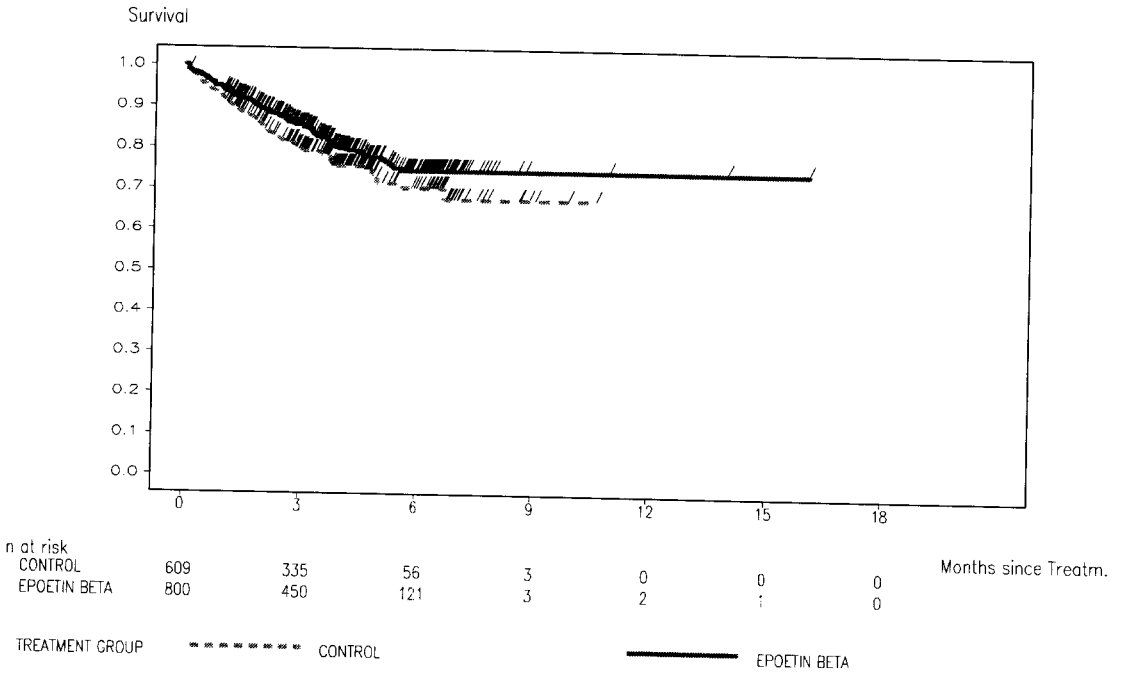
In the pooled population the number of malignancy progressions per patient year was lower in the epoetin beta group than in the control group (3.40 vs 3.69). The average follow-up time per patient was 0.27 years in the control group and 0.29 years in the epoetin beta group.

In the subgroup of patients with solid organ tumors, the number of malignancy progressions per patient year was lower in the epoetin beta arm (3.38) compared with the control arm (4.33) by almost one event per patient year. In the subgroup of patients with hematological tumors, the number of malignancy progressions per patient year was similar in the epoetin beta arm (3.41) and the control arm (3.28).

A Kaplan-Meier graph for the pooled population is provided in Figure 6. The two curves are separated, suggesting a potential advantage for epoetin beta in comparison with the control group with regard to malignancy progression. The log-rank test confirmed this difference ($p<0.05$).

Figure 6 Time to Malignancy Progression, Including All Events until Day 28 after End of Treatment

ekm21tp28_3030 – Duration of Time to PD – All Events within 28 Days after Treatment End
Protocol: CDP10130
Analysis: SAFETY POPULATION – CONTROLLED STUDIES
Filter applied: WHERE SAFCOD EQ 1 AND PROTO IN (MF4249 MF4250 MF4252 MF4253 MF4266 MF4313 MF4321 MF4421 MF4467)



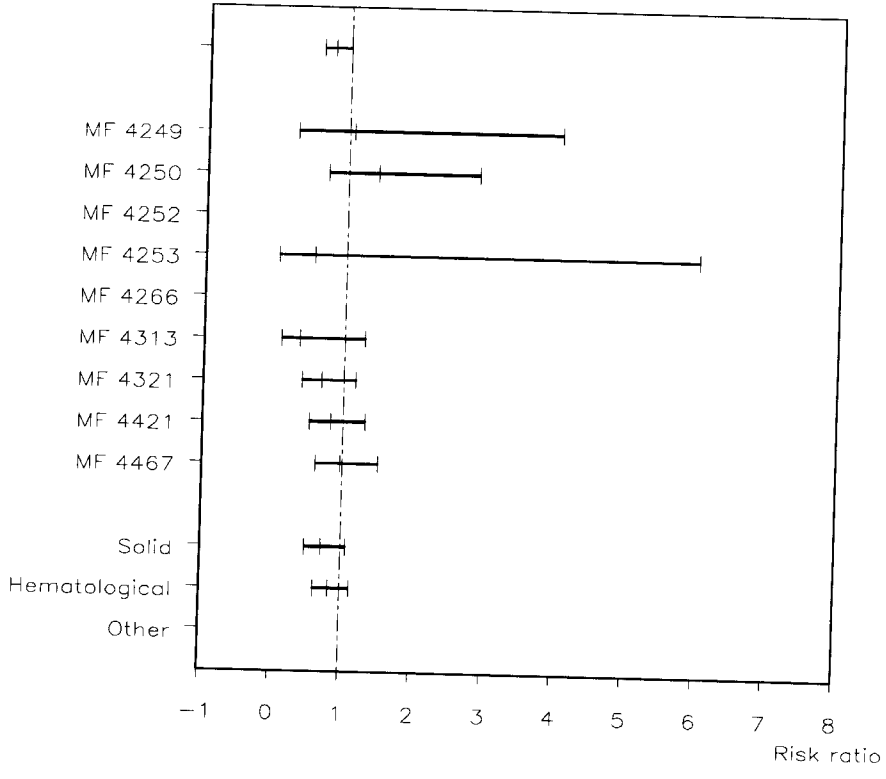
km21tp28: Produced by nendelv on 17MAR04

A summary of the underlying risks of malignancy progression measured by the hazard ratio (relative risk) in all individual studies is provided in Figure 7.

Figure 7 Summary of Hazard Rate of Time to Malignancy Progression (Kaplan-Meier Estimates and Cox Regression) Including all Events until Day 28 after end of Treatment

Esurv21tp28_3030 Hazard Ratio and 95% Confidence Intervals for Time to Progression by Subgroup – Events until Day 28

Protocol(s): CDP10130
Analysis: SAFETY POPULATION – CONTROLLED STUDIES
Filter applied: WHERE SAFCOD EQ 1 AND PROTO IN ('MF4249' 'MF4250' 'MF4252' 'MF4253' 'MF4266' 'MF4313' 'MF4321' 'MF4421' 'MF4467')



Category	Subgroup	N	Lower confidence limit	Estimate	Upper confidence limit
Total		1409	0.62	0.79	1.00
Study	MF 4249	116	0.28	1.07	4.03
	MF 4250	144	0.72	1.43	2.86
	MF 4252	54	.	.	.
	MF 4253	109	0.05	0.55	6.01
	MF 4266	20	.	.	.
	MF 4313	146	0.10	0.36	1.29
	MF 4321	218	0.40	0.69	1.17
	MF 4421	259	0.52	0.83	1.32
	MF 4467	343	0.62	0.97	1.51
Tumor Class	Solid	613	0.48	0.72	1.07
	Hematological	791	0.62	0.84	1.13
	Other	5	0.00	0.00	.

surv21tp28: Produced by nendelv on 17MAR04

There was no sign of an increased risk of malignancy progression after epoetin beta treatment in the pooled analysis. With regards to study MF4252, there were not enough events to estimate a hazard rate. Similarly, no hazard estimate was given for study MF4266 because of lack of events in the epoetin treatment arm. In two studies, the hazard ratio was about one, in four studies it was below one, and in one study it was above one. The results in the subgroups of patients with solid organ tumors and hematological tumors were consistent with the overall results. The results of these analyses do not demonstrate evidence of an adverse effect on tumor progression.

3.4 Thromboembolic events

3.4.1.1 Incidence of Thromboembolic Events

All reported thromboembolic events and the frequency of patients affected are described in table 14.

Table 14 Incidence and Type of Thromboembolic Events

Body System/	CONTROL N = 609 No. (%)	EPOETIN BETA N = 800 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	27 (4)	49 (6)
Total Number of AEs	29	53
DEEP THROMBOPHLEBITIS LEG	3 (<1)	7 (<1)
PULMONARY EMBOLUS	2 (<1)	8 (1)
ANGINA PECTORIS	4 (<1)	4 (<1)
THROMBOSIS	1 (<1)	6 (<1)
MYOCARDIAL INFARCT	3 (<1)	3 (<1)
CEREBRAL ISCHEMIA	1 (<1)	4 (<1)
MYOCARDIAL ISCHEMIA	2 (<1)	3 (<1)
THROMBOPHLEBITIS	-	4 (<1)
CEREBRAL HEMORRHAGE	2 (<1)	1 (<1)
THROMBOPHLEBITIS OF THE LEG	1 (<1)	2 (<1)
CEREBROVASCULAR ACCIDENT	2 (<1)	-
SUPERFICIAL THROMBOPHLEBITIS	-	2 (<1)
THROMBOPHLEBITIS OF THE ARM	2 (<1)	-
ARTERIAL THROMBOSIS OF THE LEG	-	1 (<1)
CEREBRAL THROMBOSIS	-	1 (<1)
DEEP THROMBOPHLEBITIS	-	1 (<1)
EMBOLUS	-	1 (<1)
EMBOLUS LOWER EXTREMITY	-	1 (<1)
INTRACRANIAL HEMORRHAGE	1 (<1)	-
PERIPHERAL VASCULAR DISORDER	1 (<1)	-
THROMBOSIS ARM	-	1 (<1)
THROMBOSIS LEG	-	1 (<1)
UNSTABLE ANGINA PECTORIS	1 (<1)	-
VASCULITIS	-	1 (<1)
Total Number of AEs	26	52
DISSEMINATED INTRAVASCULAR COAGULATION	2 (<1)	-
INTESTINAL NECROSIS	-	1 (<1)
INJECTION SITE THROMBOSIS	1 (<1)	-

3.4.1.2 Serious Thromboembolic Events

More serious thromboembolic events were reported for patients treated with epoetin beta (table 15). However, as shown in Table 16, the proportion of subjects who died as a result of a thromboembolic event was the same (1.1%) in both treatment groups.

Table 15 Serious Thromboembolic Events (all events included)

Body System/ Adverse Event	CONTROL N = 609 No. (%)	EPOETIN BETA N = 800 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	16 (3)	41 (5)
Total Number of AEs	17	44
PULMONARY EMBOLUS	2 (<1)	8 (1)
DEEP THROMBOPHLEBITIS OF THE LEG	2 (<1)	7 (<1)
THROMBOSIS	1 (<1)	6 (<1)
MYOCARDIAL INFARCT	3 (<1)	3 (<1)
CEREBRAL ISCHEMIA	1 (<1)	4 (<1)
ANGINA PECTORIS	1 (<1)	2 (<1)
CEREBRAL HEMORRHAGE	2 (<1)	1 (<1)
THROMBOPHLEBITIS	-	3 (<1)
MYOCARDIAL ISCHEMIA	-	2 (<1)
ARTERIAL THROMBOSIS OF THE LEG	-	1 (<1)
CEREBRAL THROMBOSIS	-	1 (<1)
CEREBROVASCULAR ACCIDENT	1 (<1)	-
EMBOLUS	-	1 (<1)
EMBOLUS LOWER EXTREMITY	-	1 (<1)
INTRACRANIAL HEMORRHAGE	1 (<1)	-
PERIPHERAL VASCULAR DISORDER	1 (<1)	-
SUPERFICIAL THROMBOPHLEBITIS	-	1 (<1)
THROMBOSIS LEG	-	1 (<1)
VASCULITIS	-	1 (<1)
DISSEMINATED INTRAVASCULAR COAGULATION	2 (<1)	-
INTESTINAL NECROSIS	-	1 (<1)

Table 16 Serious Thromboembolic Events Leading to Death (all events included)

Body System/ Adverse Event	CONTROL N = 609 No. (%)	EPOETIN BETA N = 800 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	7 (1)	9 (1)
Total Number of AEs	7	9
CARDIOVASCULAR SYSTEM		
Total Pts With at Least one AE	7 (1)	9 (1)
MYOCARDIAL INFARCT	3 (<1)	3 (<1)
CEREBRAL HEMORRHAGE	2 (<1)	-
CEREBRAL ISCHEMIA	-	2 (<1)
PULMONARY EMBOLUS	-	2 (<1)
CEREBRAL THROMBOSIS	-	1 (<1)
CEREBROVASCULAR ACCIDENT	1 (<1)	-
INTRACRANIAL HEMORRHAGE	1 (<1)	-
MYOCARDIAL ISCHEMIA	-	1 (<1)
Total Number of AEs	7	9

Percentages are based on N. Percentages not calculated if N < 10.

3.4.2 Subgroup Analysis

A subgroup analysis was conducted by study and by type of cancer (solid organ or hematological). There were no major differences between study populations or with cancer type with regard to frequency of thromboembolism between the epoetin beta and the control group, in particular with regard to events by patient years.

In most of the individual studies, there was a slightly higher number of events per patient year in the epoetin beta treatment group compared with the control group, and this is also seen for the crude event rate in the individual studies as well as in the pooled population.

However, in the pooled analysis of events per patient year, this difference disappears and the number of events per patient year is 3.17 in the epoetin beta group and 3.36 in the control group. Therefore, the observation of a higher crude rate in the epoetin beta group may be biased based on differences in observation time.

It has not been possible to conduct any other sub group analysis of the data according to other known risk factors associated with thromboembolism at this time.

3.4.3 Discussion

The meta-analysis performed on pooled results from clinical trials in patients with solid organ or hematological tumors showed no evidence of a negative effect on survival or tumor progression. Of note, there was a trend towards a reduced risk of progression of disease with epoetin beta treatment (HR=0.79). There was a small increase in the incidence of thromboembolic events in cancer patients receiving epoetin (6% on epoetin beta versus 4% on placebo). The higher crude rate for epoetin beta compared to control disappeared in the subgroup analysis when normalized for patient years of observation. A limitation of these data is the relatively short follow-up, therefore Section 4 reviews longer follow-up on one large study with epoetin beta.

4. SURVIVAL UPDATE IN STUDY MF4467

4.1 Methods

Study MF4467 was a double-blind, placebo-controlled study of epoetin beta in the treatment of anemia in patients with lymphoid malignancies (non-Hodgkin's lymphoma, chronic lymphocytic leukemia, multiple myeloma). The study was conducted between June 1997 and December 1999. The primary endpoint of the study was transfusion-free survival between weeks 5 and 16 after the start of study treatment. The results of the study showed significantly better transfusion-free survival in the patients treated with epoetin beta (relative risk reduction 43%; $p = 0.0012$) compared with patients treated with placebo. An additional survival update was obtained on all available patients.

4.2 Results

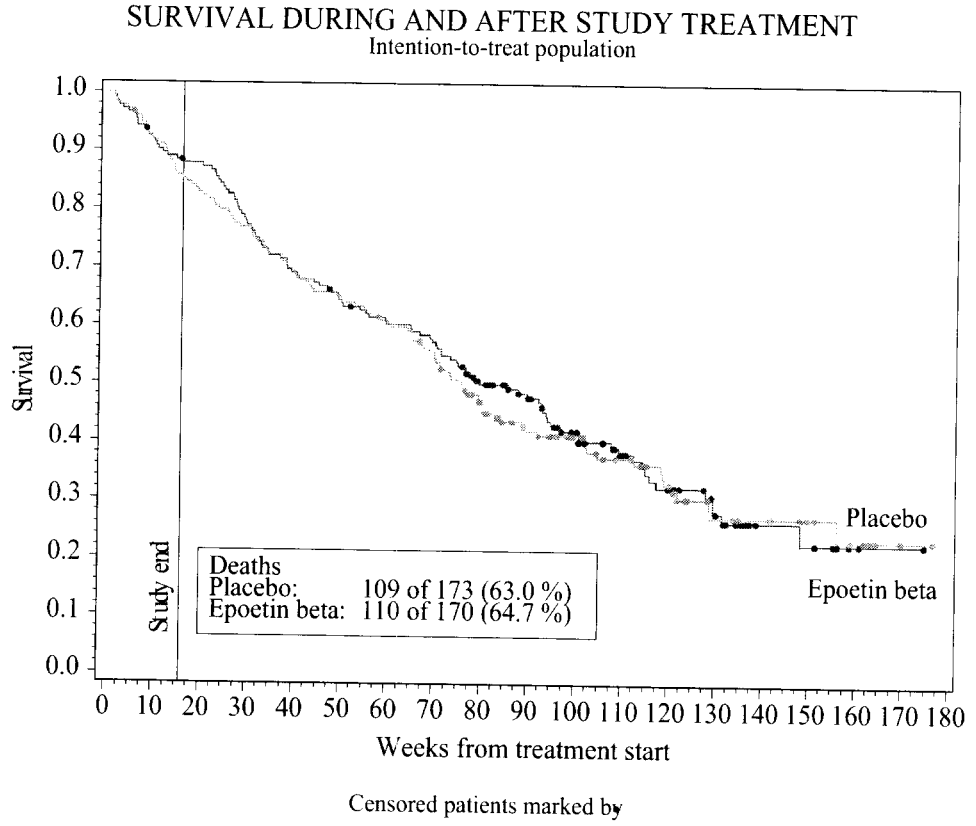
There were 170 patients in the epoetin beta treatment group and 173 patients in the placebo group included in this analysis. In the active treatment group 110 patients died by the end of follow up and 60 patients were censored for the analysis. In the placebo group, 109 patients died and 64 patients were censored. Median survival was 17.4 months in the epoetin beta and 18.3 months in the placebo group (see table 17).

Table 17 Overview of Survival Analysis Results (Study MF4467 Follow-up)

	Epoetin beta	Placebo
N	170	173
Number of events	110 (64.7%)	109 (63.0%)
Number of censored observations	60 (35.3%)	64 (37.0%)
Median survival (months)	17.4	18.3

Kaplan-Meier curves for survival were performed in both treatment groups (see Figure 8). The censoring pattern was similar in both treatment groups and started after approximately 18 months.

Figure 8 Kaplan-Meier curves for survival



The curves are similar in both treatment groups and the logrank test did not indicate differences in survival between the groups (p=0.76).

4.3 Discussion

In order to obtain longer term follow-up on survival than available in the meta-analysis, a survival update was conducted for study MF4467. There was no difference in survival between patients treated with epoetin beta and placebo. These data provide additional

evidence that treatment with epoetin beta does not have an untoward effect which manifests late in the treatment of cancer patients.

5. CONCLUSIONS

Data from a recent study, MF4449, showed decreased local progression free survival in head and neck cancer patients treated with radiation therapy and epoetin beta compared to patients receiving radiation therapy with placebo. These findings contrasted with previous clinical experience in cancer patients with anemia. To assess if the findings in this study indicated a change in the benefit-risk profile in cancer patients receiving epoetin beta, a comprehensive review focusing on Roche epoetin beta clinical data was performed. Few, if any, of these data analysis including those from multiple other studies of epoetin beta for the treatment of cancer, suggest an adverse survival effect for epoetin beta (meta-analysis of the clinical studies suggest a small advantage for progression of disease). Finally, some data from study MF4449 show imbalances in important baseline covariates that may have confounded the study.

We conclude that the large majority of existing data suggest that epoetin beta does not adversely effect tumor progression or survival in cancer patients. The most likely explanation for the adverse outcomes observed in MF4449 are factors independent of epoetin beta.